Impulse control disorders in Parkinson's disease: don't set your mind at rest by self-assessments

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Abstract: BACKGROUND AND PURPOSE: Impulse control disorders (ICDs) and related conditions in Parkinson's disease (PD) patients are frequent, disabling and sometimes devastating neuropsychiatric behaviors. Current knowledge on the prevalence of ICDs in PD is mainly based on assessments with questionnaires or patient interviews. This study was designed to evaluate the reliability of self-assessed ICDs and related conditions in PD by exploring the agreement between self-assessment of ICDs and related conditions in PD patients on the one hand and the estimation of their caregivers on the other hand. METHODS: After a short validation study of a novel ICD screening questionnaire, a cross-sectional study in 150 PD patients was performed. All patients filled out the self-assessment version of a screening questionnaire for ICDs, and caregivers completed an adapted version (n = 64). RESULTS: When comparing self-assessments of PD patients and ratings by their caregivers, significant differences with regard to the estimated prevalence of hypersexuality (55% vs. 17%), dopamine dysregulation syndrome (31% vs. 3%) and punding (22% vs. 9%) were found. CONCLUSIONS: Patients underestimate the presence and severity of some ICDs and related conditions, which shows how important assessments with caregivers are. After all, ICDs are probably much more frequent in PD than previously reported.

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Abstract

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Methods: After a short validation study of a novel ICD screening questionnaire, we performed a cross-sectional study in 150 PD patients. All patients filled out the self-assessment version of a screening questionnaire for ICDs, and caregivers completed an adapted version (n=64).

Results: When comparing self-assessments of PD patients and ratings by their caregivers, we found significant differences with regard to the estimated prevalence of hypersexuality (55% vs. 17%), dopamine dysregulation syndrome (31% vs. 3%), and punding (22% vs. 9%).

Conclusions: Patients underestimate the presence and severity of some ICDs and related conditions, which shows how important assessments in caregivers are. After all, ICDs are probably much more frequent in PD than previously reported.

Introduction

Impulse control disorders (ICDs) and related conditions in Parkinson's disease (PD) comprise pathological, repetitive behaviors including hypersexuality, compulsive shopping, compulsive eating, pathological gambling, furthermore punding and dopamine dysregulation syndrome.[1,2] Punding refers to stereotyped, repetitive, purposeless behaviors, and dopamine dysregulation syndrome is defined by compulsive misuse of dopaminergic drugs. These behavioral disorders are often related to dopaminergic stimulation – particularly by dopamine agonists - and are thus considered mostly iatrogenic.[3] Although ICDs often have a devastating impact on quality of life of patients and their spouses, it was long after the introduction of dopamine agonists that the spectrum of ICDs in PD attracted interest and the association with dopaminergic medication was identified. ICDs are an independent predictor of reduced quality of life, in particular emotional well-being, and are independently associated with increased disability (Phu et al., 2014).

The largest epidemiological study on ICDs (gambling, compulsive sexual behavior, compulsive buying, binge-eating) in PD patients was cross-sectional, multicenter, included 3090 patients and applied various validated tests and interviews to assess these behaviors.[4] The authors found ICDs in 13.6% of the patients: gambling in 5.0%, hypersexuality in 3.5%, compulsive shopping in 5.7%, and compulsive eating in 4.3%. A more recent single-center, cross-sectional prevalence study in 805 PD patients found ICDs in 8.1%.[5]

Ironically, while the increasing awareness of ICDs and related conditions in PD promoted the development and validation of specific ICD questionnaires, these very questionnaires have never been analyzed for their reliability. Indeed, based on own observations with self-rating ICD questionnaires, the presence of some ICDs repeatedly escaped our notice, but became evident when we had the opportunity to observe the patient for a longer period (e.g. during hospitalization) or even more when expanding history-taking to caregivers, spouses, or relatives (here referred to as "caregivers"). Therefore, we hypothesized that self-reported frequencies of ICDs are lower than the

frequencies of ICDs reported by caregivers. To this end, we administered an ICD questionnaire to both PD patients and their caregivers, in order to determine how often certain ICDs and related conditions are underestimated by PD patients. In addition, we aimed at identifying potential associates of ICDs.

Methods

This study was performed at the movement disorders outpatient unit of the Department of Neurology, University Hospital of Zurich, Switzerland, between March 2010 and February 2012. Within a cross-sectional design, we administered the same questionnaire to PD patients and their caregivers, if available. The study was approved by the Ethics Committee of the Canton of Zurich (Kantonale Ethikkommission), and all patients consented into study participation.

ICDs and related conditions (ICDRC) questionnaire: introduction and brief validation. Based on international definitions of the respective ICDs and related conditions, we developed a structured and short screening questionnaire assessing pathological gambling, compulsive shopping, compulsive eating, hypersexuality, punding and dopamine dysregulation syndrome (Suppl. Figure).[6] The ICDRC questionnaire which was distributed to caregivers was slightly adapted by replacing "you-questions" by "she- or he-questions". The questionnaire consists of 12 questions (five point Likert scale, 0-4), each evaluating the frequency of the respective behavior and the consecutive psychosocial consequences. Each ICD-related behavior was represented by 2 questions.

In a brief validation study, we compared this novel ICDRC questionnaire against full clinical ICD assessment in PD patients. The questionnaire was distributed to 85 patients, and 78 returned a fully completed questionnaire. In all these patients, the last author screened at every visit for ICDs by using internationally accepted criteria as summarized by Voon and Fox.[6] The last visit prior to the distribution of questionnaires was used for this study. Another team (HBV, ES and POV) independently collected and analyzed the results. To calculate sensitivity and specificity of the

questionnaire for each ICD, we considered an ICD present if at least one of the two questions for an ICD or a related behavior counted 3 or 4 points on the Likert scale, stating that this behavior is often or regularly present. The assessed sensitivities and specificities of the ICDRC questionnaire are summarized in Table 1. For each ICD or related condition, we found acceptable values except for dopamine dysregulation syndrome. When accepting – as we did for other behaviors - that dopamine regulation syndrome is present if either of the two questions was positive (Likert scores 3 or 4), specificity was too low (38%). Therefore, for dopamine dysregulation syndrome, both questions must be answered positively. These scoring rules were used for the analysis of the main part of the present study.

Frequencies of ICDs and related conditions (ICDRC) in PD patients and in caregivers. For the cross-sectional comparative prevalence study, we distributed the ICDRC questionnaire to 175 consecutive PD patients from our movement disorders outpatient clinic, and finally included 150 patients who returned fully completed questionnaires. We included patients with all stages of PD, irrespective of treatment. Exclusion criteria were atypical Parkinson disorders, comorbid psychiatric disorders, and dementia (Montreal Cognitive Assessment Scale <21/30) (Dalrymple 2010). These patients were different from those who have been included for validation procedures. The diagnosis of PD was made along international criteria,[7] and patients with atypical, secondary or unclear Parkinson disorders were excluded. When available, the questionnaires were also distributed to caregivers, and 64 of those returned fully completed questionnaires. We distributed questionnaires only to caregivers who regularly accompanied patients to our outpatient clinic. This approach was chosen deliberately because we wanted ensure that caregivers were well informed about the patients. In this line, caregivers who claimed being not so well informed about the patient and his habits were not invited to participate.

~~***Associations of ICDs or related behaviors with PD-related features.*** In all patients, we assessed~~

~~disease duration, motor symptoms by the motor part of Unified Parkinson's Disease Rating Scale (UPDRS III), the predominant side of PD symptoms, the predominant motor features of PD (akinetic-rigid versus tremor-dominant), the presence or absence of motor fluctuations, total L-dopa equivalent doses (LED) for all dopaminergic drugs and for dopamine agonists only, and the dosages of the neuroleptics clozapine and quetiapine.[8,9] Furthermore, we assessed psychiatric symptoms with the Hospital Anxiety and Depression Scale (HADS), excessive daytime sleepiness with the Epworth sleepiness scale (ESS), fatigue with the Fatigue Severity Scale (FSS), and apathy with the Apathy Evaluation Scale (AES). To examine whether ICDs or related behaviors are associated with any of these motor and non-motor signs or to medication, we used the ICD scores from caregivers, and therefore included the n=64 population in this analysis.~~

Statistical analysis. Statistical analysis was conducted with SPSS version 12.0. Statistical significance level was set at $P \leq 0.05$. ~~To assess associates of specific ICD, we used ordinal logistic regression analysis to search for variables significantly associated with the Likert scale, including sex, disease type, affected body side, and presence of dyskinesia as factors, and age, UPDRS III, Hoehn & Yahr, disease duration, total LED, LED of levodopa and dopamine agonists, HADS scores, and ESS and FSS scores as covariates. Other tests used in this study have been introduced above.~~). To examine whether the prevalence as given by the caregivers differed from self-estimated data, we applied non-parametric related-samples McNemar tests in the 64 subjects with 2 complete datasets. We also checked whether patients with data from caregivers were different from those without such data.

Results

Demographic and clinical characteristics. Table 2 gives a detailed overview on the demographic and clinical characteristics of the included 150 PD patients. The scores for ICDs and related

behavior did not differ between the 64 patients with additional ratings of their caregivers and the remaining 86 patients. The two groups differed, however, with regard to disease type, frequency of dyskinesia, fatigue severity, and dopaminergic treatment.

ICDRC questionnaire: comparison of self-rating and estimation by caregivers. As shown in Figure 1, the comparison of self-rated frequencies of ICDs and related conditions by PD patients and the estimation by their caregivers revealed striking differences. Specifically, caregivers considered pathological gambling (p=0.01), hypersexuality (p<0.001), compulsive shopping (p<0.001), punding (p<0.001) and dopamine dysregulation syndrome (p<0.001) to occur with significantly higher frequencies than indicated by the patients (Figure 1A). When contrasting the two perspectives regarding the presence or absence of specific ICDs (i.e. ≥3 or <3 points on the Likert scale, respectively), the observed discrepancy mostly went in one direction: Disagreement between two statements usually meant that the caregiver considered an ICD to be present, whereas the PD patient claimed its absence (Figure 1B). We observed such an assumed underestimation by PD patients for the presence of hypersexuality (11 vs. 25; $p < 0.001$), punding (6 vs. 14; $p = 0.008$) and dopamine dysregulation syndrome (2 vs. 20; $p < 0.001$). On the other hand, underestimation by the caregiver (or overestimation by the PD patient) occurred more rarely.

~~***Associates of ICDs and related conditions.*** When screening for such associate PD parameters by multivariate regression analyses, we found significant associations of both LED of dopamine agonists (p<0.001) and HADS (p<0.05) with the total sum score of all ICDs and related conditions. We found no similar associates of pathological gambling and compulsive medication use. However, total hypersexuality scores correlated positively with male sex (p<0.05), total compulsive shopping scores with LED of dopamine agonists (p<0.02), and total punding scores with the severity of depressive symptoms (HADS D; p<0.001).~~

Conclusions

With the increased awareness of neurologists that ICDs and related conditions are burdensome and might cause significant psychosocial and medicolegal problems, self-assessment questionnaires are increasingly used to screen for ICDs in Parkinson patients. Voon and Fox reviewed the prevalence of ICD in the literature and found the following values: pathological gambling in 2.5%, compulsive shopping in 0.4-1.5%, in hypersexuality in 2.5% of PD patients, with an overall prevalence of ICDs and related conditions of 5.9% (Voon and Fox, 2007). Later on, Weintraub and colleagues performed a large cross-sectional study in 3090 patients and found gambling in 5.0%, hypersexuality in 3.5%, compulsive shopping in 5.7%, and binge-eating disorder in 4.3% (Weintraub et al., 2010). In a case-controlled study in 311 participants, the prevalence of punding was found to be 4.8% (Weintraub et al., 2009). In clinical practice, differences in reporting ICDs or related conditions between caregivers and patients are often evident. This is - to our best knowledge - the first study to systematically address this issue.

In agreement with our hypothesis, we found a markedly higher prevalence of hypersexuality (55% vs. 17%), punding (22% vs. 9%) and dopamine dysregulation syndrome (31% vs. 3%) when assessed in caregivers compared to patients' estimations and previously reported prevalences. Also, the overall severities of most ICDs and related conditions as assessed by the Likert scale are higher when indicated by caregivers. The reasons for this difference remain speculative. A possible cause might be an aberrant self-awareness of ICD-related behaviors in patients. However, Mack et al. found no differences in self-awareness between patients with or without ICDs, and patients were aware of their impulsivity.[10] Notably, this study was limited by a rather low number of 17 patients per group.

There might be an association between alexithymia and ICDs in PD patients.[11] Alexithymia is a personality trait causing difficulties in identifying their own feelings, describing them to others,

showing external oriented cognitive style and little ability for introspection. In a recent study, alexithymia was identified as an independent risk factor for impulsive-compulsive disorders in Parkinson patients.[12] Another cause of underreporting might be deliberate withholding of relevant information due to the often humiliating nature of these symptoms. In this line, Farnikova and colleagues examined personality characteristics in PD patients with and without ICD.[13] They found higher scores of social introversion subscales in PD patients with ICDs which indicates lower self-esteem.

We certainly cannot rule out that overestimation of ICDs by caregivers might contribute to the observed discrepancies. Dopamine dysregulation syndrome could serve as an example for such an assumption: many patients prefer dyskinesia over hypokinetic motor states. The latter are often associated with pain, depressive symptoms, and apathy. For the caregivers, dyskinesia may constitute a bigger problem than OFF-states because they can be associated with increased danger of falls and with patients' overestimation of their real abilities. Thus, caregivers might feel that their partner should decrease the dosage of his dopaminergic medication.

There are several limitations of this study. The number of included patients was small, but the differences between patients and their caregivers remained nevertheless impressive and significant. To fully assess clinical associates of ICDs and related conditions, however, this study was underpowered. Furthermore, our questionnaire did not include all ICDs and related conditions. In clinical practice, the questionnaire we used will not substitute a thoroughly validated screening. The most commonly used Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), designed by Weintraub and colleagues[14] has been validated in a large cohort. Still, the shortness of our questionnaire and the use of a Likert scale for the assessment of intra-item grading might be regarded as an advantage of the present instrument.

Altogether, our results underline the importance of assessing ICDs and related conditions by

history-taking or administering questionnaires not only in patients, but also in spouses, relatives or caregivers. Thus, clinicians should not set their mind at rest by self-assessments when dealing with these burdensome and sometimes even dangerous behaviors.

Abbreviations

AES apathy evaluation scale, ESS Epworth sleepiness scale, FSS fatigue severity scale, HADS hospital anxiety and depression scale, HS hypersexuality, ICDs impulse control disorders, LED Levodopa equivalent dose, PG pathological gambling, PD Parkinson's disease, QUIP questionnaire for impulsive-compulsive disorders in Parkinson's disease. UPDRS III unified Parkinson's disease rating scale, part III (motor assessment).

Table 1. Sensitivity and specificity of questions for impulse control disorders (ICDs) and related conditions of the ICDRC questionnaire. For all calculations, questionnaire-driven data were interpreted positive (i.e. the ICD or related condition is considered present) if at least one of the two questions were scored with 3 or 4 points. (*For dopamine dysregulation syndrome, we adapted this calculation to increase specificity and scored this behavior only as present if both questions were scored with 3 or 4 points). Right and false positive outcomes were assessed by comparing these questionnaire data to structured interviews along international recommendations.[6]

	Sensitivity	**Specificity**
Pathological gambling	83%	97%
Hypersexuality	69%	95%
Compulsive shopping	75%	100%
Binge eating	67%	95%
Punding	60%	100%
Dopamine dysregulation syndrome	80%*	69%*

Table 2. Demographic and clinical characteristics of 150 patients with Parkinson's disease. Data are compared between patients with and without additional ratings of ICDs and related conditions by relatives or caregivers.

	PD patients with data from caregivers (n = 64)	**PD patients without data from caregivers (n = 86)**	***p***
Demographic data			
Age [y]	67 ± 9	69 ± 10	0.18
Sex, female	19 (30%)	38 (44%)	0.09
Parkinson-related data			
Disease type			***0.01***
tremor-dominant	10 (16%)	32 (37%)	
akinetic-rigid	45 (70%)	43 (50%)	
equal	9 (14%)	11 (13%)	
Predominantly affected side, left	33 (52%)	41 (48%)	0.63
Disease duration [y]	11.3 ± 5.6	10.1 ± 7.3	0.29
UPDRS III	24.7 ± 10.5	25.8 ± 12.5	0.57
Hoehn & Yahr	2.2 ± 0.5	2.2 ± 0.7	0.90
Dyskinesia	60%	34%	***0.004***
Dopaminergic treatment			
Total LED	913 ± 427	692 ± 457	***0.003***
LED $_{\text{levodopa}}$	568 ± 262	431 ± 276	***0.002***
LED $_{\text{dopamine agonists}}$	188 ± 199	159 ± 170	0.35
Non-motor symptoms			
ICDRC questionnaire sum scores	8.6 ± 6.1	7.6 ± 5.3	0.32
Pathological gambling	0.4 ± 0.9	0.3 ± 0.9	0.74
Hypersexuality	1.6 ± 1.9	1.4 ± 1.5	0.41
Compulsive shopping	0.8 ± 1.2	0.7 ± 1.2	0.44
Compulsive eating	1.7 ± 2.1	1.1 ± 1.5	0.07
Punding	1.3 ± 1.7	1.1 ± 1.6	0.48
Dopamine dysregulation syndrome	2.8 ± 2.2	3.0 ± 2.3	0.52
HADS anxiety scores	6.5 ± 4.0	6.3 ± 4.0	0.78
HADS depression scores	6.6 ± 4.5	6.4 ± 3.9	0.74
ESS scores	9.0 ± 6.1	9.2 ± 4.8	0.88
Daytime sleepiness (ESS ≥ 10)	26 (41%)	41 (48%)	0.41
FSS scores	4.6 ± 1.5	4.0 ± 1.7	***0.03***
Fatigue (FSS ≥ 4.0)	38 (59%)	42 (49%)	0.25

Figure 1. The impulse control disorders and related conditions (ICDRC) questionnaire.

Figure 2. A. Impulse control disorders and related conditions (ICDRC) questionnaire sum scores. Higher sum scores indicate higher frequency and severity of ICDs. Vertical lines indicate standard deviations. **B.** Estimation of presence of ICDs. White color: agreement between patients and caregivers. Black color: underestimation of the presence of ICDs by patients (alternative interpretation: overestimation by caregivers). Grey color: overestimation of the presence of ICDs by patients (alternative interpretation: underestimation by caregivers). *: $p<0.05$. **: $p<0.01$, ***: $p<0.001$.

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